

**Biomarkers of Oxidative and Inflammatory Stress and
the Risk for Atherosclerosis in Astronauts during and
after Long-Duration Spaceflight**

Human Research Program Informed Consent Briefing

PI: Steven H. Platts, PhD

Defining the Relationship between Biomarkers of Oxidative and Inflammatory Stress and the Risk for Atherosclerosis in Astronauts during and after Long-Duration Spaceflight

Short Title: Cardio Ox

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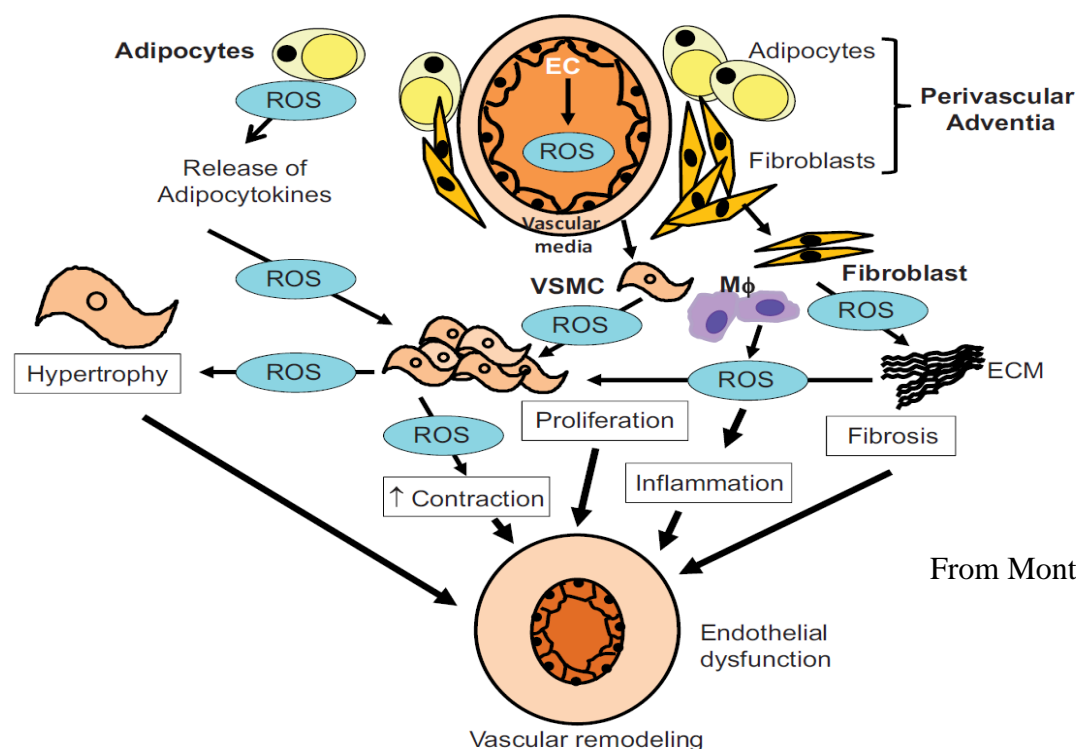
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Science Background

- It is not known if astronauts participating in long-duration space flight and exploration missions beyond low Earth orbit are at an elevated risk for cardiovascular diseases, in particular atherosclerosis.
- Data from Earth/clinical studies suggest that the space flight environment has the potential to increase cardiovascular risks due to oxidative stress.
- Reactive oxygen species (ROS, or free radicals) are produced naturally by the body and are present in environment, as are antioxidants.
- Disrupting the balance between ROS and anti-oxidants increases risk of oxidative damage (cellular components, DNA) and inflammation.
- Stress, radiation, and poor diet practices have been shown to disrupt this balance and may present during spaceflight.



- Markers of oxidative and inflammatory stress have been closely linked to the development of atherosclerosis in clinical populations on Earth.
- Impaired arterial function and thickening of the carotid artery are two well-characterized sub-clinical indicators of the development of atherosclerosis.

Science Background

- The risk of atherosclerosis development is covered under HRP HHC Cardiovascular Research Gap CV8.
 - NASA HRP Risk of Cardiac Rhythm Problems: “GAP-CV8: Can manifestations of sub-clinical or environmentally induced cardiovascular diseases during spaceflight be predicted?”

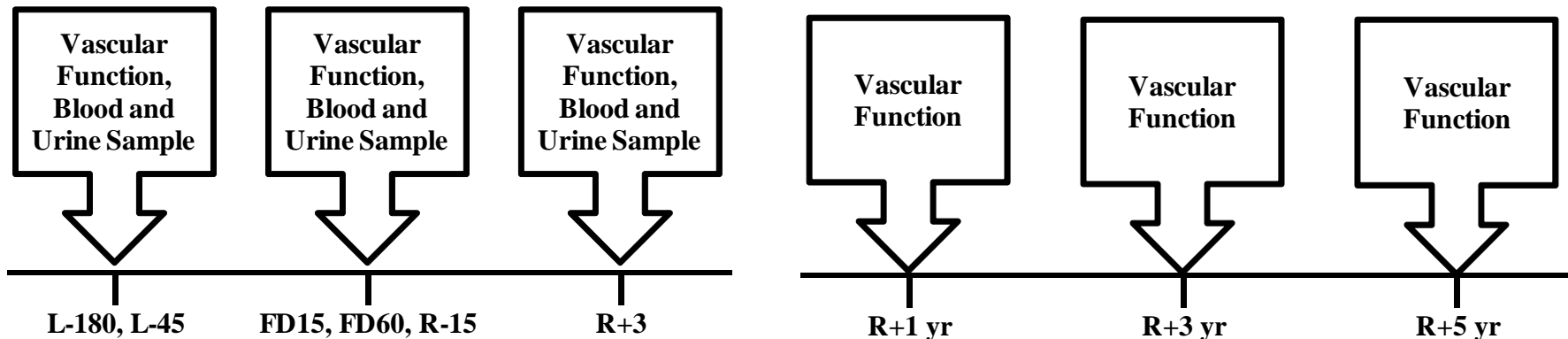
The central hypothesis is that circulating biomarkers of inflammatory and oxidative stress are elevated during spaceflight, and these will be related to longer-term changes in vascular structure and/or function.

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<div data-bbox="869 355 1218 431" data-label="Section-Header"> <h2>Objectives</h2> </div> <div data-bbox="203 511 1877 1107" data-label="List-Group"> <ol style="list-style-type: none"> 1. To determine the effects of long-duration spaceflight on biomarkers of inflammatory and oxidative stress. (Blood and urine) 2. To determine the effects of long-duration spaceflight on measures of arterial structure and function. (Ultrasound and blood pressure measures) 3. To determine how alterations in vascular structure and function relate to changes in circulating biomarkers of oxidative and inflammatory stress. 4. To monitor vascular status for up to five years after long-duration space flight. (Surveillance) </div> <div data-bbox="199 1242 1757 1424" data-label="Text"> <p>ISS most closely mimics future exploration scenarios and is the only environment available with the combination of stressors that may lead to oxidative stress/damage.</p> </div>	

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Experiment Design Overview

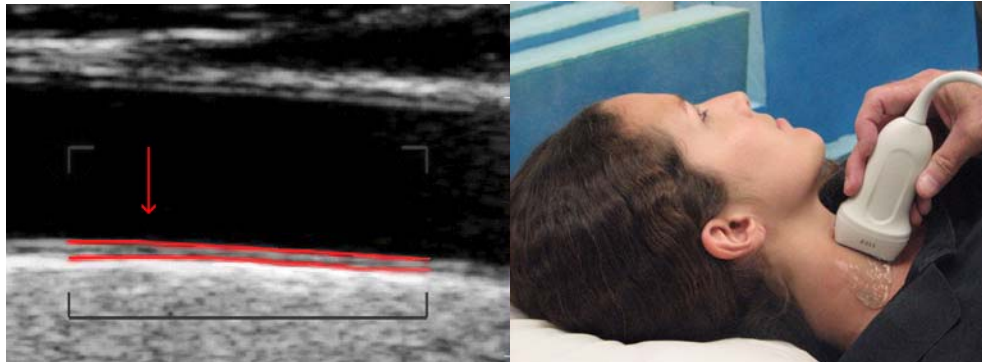
Preflight	Inflight	Postflight
Vascular Function (Ultrasound & BP measures) L-180, L-45	Vascular Function (Ultrasound & BP measures) FD15, FD60, FD180 (R-15)	Vascular Function (Ultrasound & BP measures) R+3 d
Biomarkers of Oxidative Stress and Inflammation (48-h urine collection, blood draw) L-180, L-45	Biomarkers of Oxidative Stress and Inflammation (24-h urine collection, blood draw) FD15, FD60, FD180 (R-15)	Biomarkers of Oxidative Stress and Inflammation (48-h urine collection, blood draw) R+3 d
		Vascular Function (Ultrasound measures) R+1 yr, R+3 yr, R+5 yr



Pre- and Post-Flight Test/Session Descriptions

Vascular Function: L-180, L-45, R+3

- Resting blood pressure and stroke volume/cardiac output using ultrasound
- Carotid Intima-Media Thickness (CIMT): Ultrasound measures of carotid arterial wall thickness. (arterial structure)

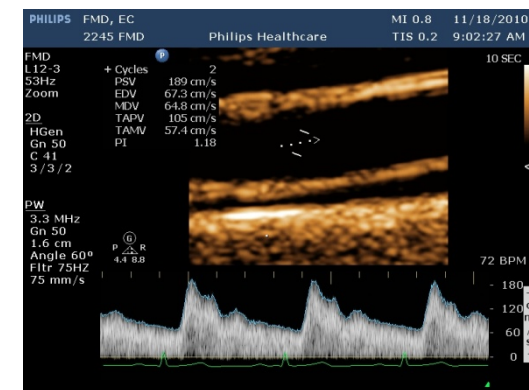
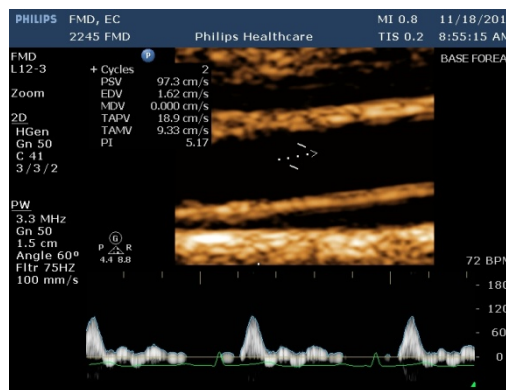
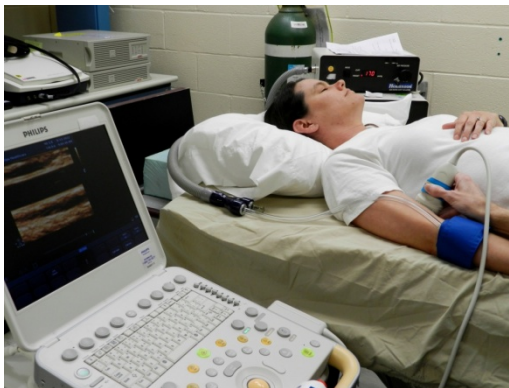


- Pulse Wave Velocity (PWV): Time required for the blood to travel from the heart to the arm, obtained using ultrasound and ECG. (arterial stiffness)

Pre- and Post-Flight Test/Session Descriptions

Vascular Function: L-180, L-45, R+3

- Flow-Mediated Dilation (FMD): Ultrasound measure of brachial artery blood flow following five minutes of blood flow occlusion using a blood pressure cuff. (arterial function)
- Sublingual Nitroglycerin (SLN): Ultrasound measure of brachial artery blood flow after receiving small dosage of nitroglycerin. (arterial function)



Pre- and Post-Flight Test/Session Descriptions

Biomarkers: L-180, L-45, R+3

- A fasting blood sample (12.5 ml) and 48-hour urine collection will be completed at each time point using standard techniques.
- These sessions will be combined with other experiments and medical requirement testing wherever possible to avoid duplication of collections.
- Wherever possible, data from other experiments and medical requirements, medication and exercise logs will be shared with existing requirements.

In-Flight Test/Session Descriptions




Vascular Function: FD15, FD60, R-15

- Resting blood pressure and stroke volume/cardiac output
- Carotid Intima-Media Thickness (CIMT), Resting Brachial Artery Diameter and Pulse Wave Velocity.
- Ultrasound measures obtained with the assistance of an ultrasound expert in the Telescience Support Center using remote guidance.



In-Flight Test/Session Descriptions

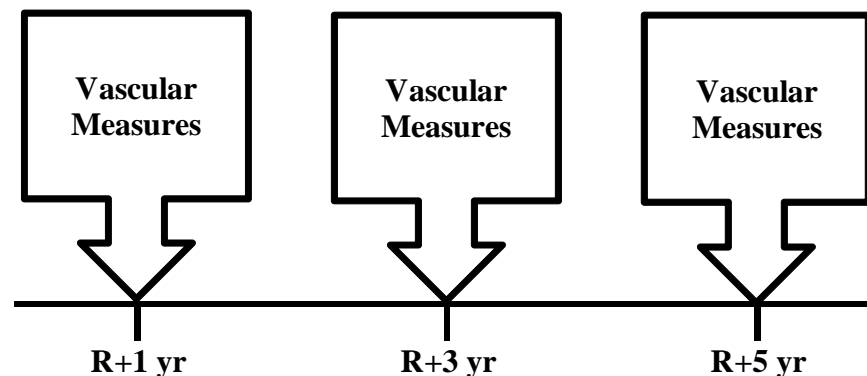
Biomarkers: FD15, FD60, R-15

- A fasting blood sample (10 ml) and 24-hour urine collection will be completed at each time point using standard techniques.
 - Urine collection will use either Urine Monitoring System or Urine Collection Devices (depending on UMS availability).
 - These sessions will be combined with other experiments wherever possible to avoid duplication of collections.
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- Wherever possible, data from other experiments, medication and exercise logs will be shared with existing requirements.

Post-Flight (Surveillance) Test/Session Descriptions

Vascular Function: R+1 yr, R+3 yr, R+5 yr (100 min/session)

- Post-flight surveillance measures (unique experimental requirement).
- Same measures as pre- and immediate post-flight.
- Will schedule in conjunction with yearly physical when possible.



Contributing Factors

- Data sharing will be requested with MRIDs specific to:
 - Radiation exposure
 - Hyperoxic exposures (EVA and pre-breathe)
 - Pre- and in-flight nutritional habits and status
 - Pre-, in-, and post-flight exercise training and testing
 - Medication usage
 - Blood pressure and cardiac output (new ocular MRID)
 - ISS environmental conditions

Expected Results

- We anticipate that markers of oxidative stress and inflammation will be elevated during flight but will return toward pre-flight baseline soon after landing.
- We expect subclinical manifestations of atherosclerosis, altered arterial structure and function, will result from space flight without symptomatic presentation.

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<div data-bbox="890 326 1197 396" data-label="Section-Header"> <h2 style="text-align: center;">Benefits</h2> </div> <div data-bbox="205 423 1862 1458" data-label="List-Group"> <ul style="list-style-type: none"> • This study will provide important information about the influence of the space flight environment on oxidative stress and inflammatory responses in astronauts participating in long duration space flight, providing information about future exploration missions and guiding plans for medical care. • This investigation is designed to determine, for the first time, whether changes in oxidative stress and inflammation are related to changes in vascular function and structure which are considered to be subclinical markers of the early stages of atherosclerosis. • While most cardiovascular investigations have been concerned with the in- and immediate post-flight consequences of space flight, this study is uniquely designed to understand the long-term consequences of space flight on cardiovascular health. • Oxidative stress, terrestrially, to lead to atherosclerosis. Most studies examine single cause stressors, our work will include multiple earth relevant stressors in combination. </div>	